Impaired gastrocolonic response and peristaltic reflex in slow-transit constipation: role of 5-HT3 pathways

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Björnsson, Einar S., William D. Chey, Forrest Hooper, Michelle L. Woods, Chung Owyang, and William L. Hasler. Impaired gastrocolonic response and peristaltic reflex in slow-transit constipation: role of 5-HT3 pathways. Am J Physiol Gastrointest Liver Physiol 283: G400–G407, 2002; 10.1152/ajpgi.00082.2001.—Colonic motility is modulated by the 5-hydroxytryptamine (5-HT3)-dependent gastrocolonic response and 5-HT3-independent peristaltic reflex. We compared descending colon tone responses to antral distension, duodenal lipid perfusion, and colonic distension after double-blind placebo or granisetron in 13 healthy volunteers and nine slow-transit constipated patients. Antral distension (100–300 ml) and duodenal lipids (3 kcal/min) evoked increases in colon tone in volunteers, which were blunted in constipated patients (P < 0.05). Granisetron (10 μg/kg) reduced responses to antral distension and lipids in volunteers and to lipids in constipated patients (P < 0.05). The ascending contraction of the peristaltic reflex was blunted in constipated patients (P < 0.05), whereas descending responses were similar. Granisetron did not modify the peristaltic reflex. Colonic responses to bethanechol were similar. Granisetron did not modify the gastrocolonic responses to antral mechanical or duodenal nutrient stimulation. Colonic transit also is modulated by local reflex activity within the colon. Recently, the colonic peristaltic reflex was characterized in a human model (5, 24). In these studies, inflation of a stimulus balloon in the colon was shown to evoke an oral ascending contraction and a caudal descending response consisting of a relaxation followed by a contraction. Abnormalities of the ascending and descending components of the peristaltic reflex in slow-transit constipation are uncharacterized.

Serotonin 5-hydroxytryptamine (5-HT3) receptors play important roles as mediators of the gastrocolonic response. 5-HT3 receptor antagonists blunt the colonic contractile response to meal ingestion (29). A further investigation reported that the 5-HT3 receptor antagonist granisetron inhibits gastrocolonic responses elicited by both antral distension and intestinal lipid perfusion (5). In contrast, the ascending and descending components of the peristaltic reflex are mediated by 5-HT3-independent pathways in healthy volunteers (5). It is unknown whether patients with slow-transit constipation exhibit specific defects in 5-HT3-dependent or -independent components of the gastrocolonic response.

The aim of the present study was to test the hypothesis that severe idiopathic slow-transit constipation is associated with impairment of extended and local reflexes that modulate colonic motor function. Specifically, we aimed to determine whether slow-transit constipation is associated with selective defects in the colonic motor responses to antral distension or duodenal lipid perfusion or in the oral or caudal components of the colonic peristaltic reflex. Furthermore, double-blind studies were performed after intravenous administration of granisetron or placebo to evaluate whether...
any defects in colonic reflex activity in patients with slow-transit constipation could be determined to be specific for 5-HT3-dependent or independent pathways. To confirm that generalized impairments in colonic tone responses were not secondary to reduced smooth muscle contractile function, colonic motor responses to the direct smooth muscle muscarinic agonist bethanechol were compared in the patients with slow-transit constipation and the healthy volunteers. Through these studies, we hoped to gain insight into the pathophysiology of idiopathic slow-transit constipation.

MATERIALS AND METHODS

Subject Populations

Nine women with chronic constipation (mean age 32 ± 4 yr, range 19–40 yr) unresponsive to fiber supplements were recruited for participation in this investigation. All patients reported severe constipation with <2 bowel movements per week for at least 1 yr. No patient reported abdominal pain as a significant symptom and none reported diarrhea. None had undergone prior gastrointestinal surgery except for two individuals who had had prior appendectomies. No patient was on any medication that could delay colonic transit or alter visceral perception. Before study inclusion, organic colonic disease had been excluded by colonoscopy or barium enema plus sigmoidoscopy and by appropriate biochemical testing (blood chemistries, thyroid chemistries, and other tests when indicated). All patients underwent colonic transit testing with radiopaque markers before study inclusion and exhibited total colonic transit times above the upper limit of the normal range (<68 h) without evidence of selective regional transit defects. None of the patients had evidence of dyssynergic defecation measured by proctography. Anorectal manometry was normal in all patients, except for two patients who exhibited slightly reduced perception of urgency.

Thirteen healthy volunteers (7 males, 6 females; mean age 31 ± 5 yr, range 20–48 yr) were recruited to serve as the control population. No healthy volunteer reported gastrointestinal complaints, none had undergone prior abdominal surgery, and none was on medications known to alter gastrointestinal motor or sensory function at the time of study.

All studies were approved by the University of Michigan Institutional Review Board. Written informed consent was obtained from all study subjects before participation.

Colonic Barostat Methodology

Isobaric determination of colonic tone was performed using an electronic barostat with recording balloons endoscopically placed in the descending colon. Recording of colonic motor activity was begun 30 min after double-blind intravenous infusion of granisetron hydrochloride (Kytril, SmithKlineBeecham Pharmaceuticals, Philadelphia, PA) 10 μg/kg or placebo vehicle on separate days in random order. Studies on the same individual were performed at least 3 days apart to minimize any residual pharmaceutical effect or motor desensitization. All subjects underwent measurement of the peristaltic reflex and the antral distension-evoked gastrocolonic response on the same day. Testing of the duodenal lipid-evoked colonic response was performed on separate days because of the prolonged nature of this response, also after intravenous granisetron or placebo in random order. On separate days, testing of the colonic smooth muscle response to bethanechol injection was compared in four healthy volunteers and four patients with slow-transit constipation.

The evening before study, subjects ingested 3.8 liters of isotonic colonic lavage solution (Co-Lyte; Reed & Carnick, Jersey City, NJ). After overnight fasting, subjects were positioned on their left side and colonoscopy was performed to the cecum after intravenous administration of the lowest dose of midazolam required to achieve conscious sedation with minimal discomfort (4–10 mg; Versed, Hoffman-La Roche, Nutley, NJ). A Teflon-coated guidewire was inserted through the biopsy channel and the colonoscope was removed. A 75-cm multilumen barostat catheter, constructed from three 14-Fr Tygon tubes fixed together, was advanced over the guidewire so that the tip reached the splenic flexure, as confirmed by fluoroscopy. Three balloons were located in a series along the distal 30 cm of the catheter, with each balloon communicating via separate lumens, as previously described in detail (5).

The middle balloon (stimulus balloon), constructed of latex and 5-cm in length, served as a distending stimulus and was inflated manually through a valve at the proximal end of the catheter. Highly compliant polyethylene proximal and distal balloons were 8 cm in length with maximal capacities of 400 ml and had a geometric coil of 15 cm from the center of the middle balloon. The proximal and the distal balloons were connected individually to an electronic barostat (Isobar-3; G & J Electronics, Toronto, Ontario, Canada) to measure changes in colonic tone. Inflation of the recording balloons was controlled by a single 700-ml cylinder within the barostat. Pressures were recorded within the cylinder apparatus. Volume and pressure output from the barostat were recorded on a paper chart (Beckman Dynograph Recorder R611; Sensor Medics, Yorba Linda, CA) and also were stored in digital form on diskette for later analysis. After a 2-h equilibrium period to allow tolerance to the balloons and recovery from sedation, subjects were positioned on their left side with knees and hips flexed, where they remained for the remainder of the study.

Gastrocolonic response assessment. To elicit the colonic response to antral distension, each subject was orally intubated with a modified nasogastric tube (18-Fr), to the end of which was attached a standard latex condom for balloon distension of the distal stomach. The balloon was 9.5 cm in length and was sutured to both ends of the catheter to ensure radial, but not longitudinal, distension on inflation. After intubation, antral placement of the inflation balloon was confirmed fluoroscopically. Before the measurement of the gastrocolonic response, the proximal colonic recording balloon was set to an operating pressure of 2 mmHg greater than the minimal distending pressure necessary to detect respiratory variations in the recorded intraballoon volume. The gastrocolonic response was induced by filling the distal gastric balloon with saline to sequential volumes of 100, 200, and 300 ml at a rate of 300 ml/min. The distal gastric balloon remained filled for 5 min after which it was deflated at 300 ml/min. Between inflations, 30-min periods of deflation were provided to allow colonic tone to return to baseline before the next distending stimulus was repeated. This protocol has been previously demonstrated to elicit reproducible increases in colonic tone (5, 24). The amplitude of the gastrocolonic response was measured as the mean volume decrease during the inflation period compared with the 5-min period preceding inflation. Latency to the development of this mechanoreceptor-mediated response was defined as the time in seconds from the onset of gastric balloon inflation to the point at which the decrease in colonic balloon volume represented 10% of the maximal volume decrease obtained during the 5-min inflation period. The maximal volume decrease was determined by the lowest volume level obtained from the analysis of volume values obtained in 1-s intervals in stan-
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To investigate the colonic response elicited by duodenal lipids, a single lumen intestinal feeding tube was placed under fluoroscopic guidance into the midduodenum for intestinal lipid perfusion on separate days from the antral distension studies. After setting the operating pressure 2 mmHg above the minimal distending pressure, changes in colonic tone were measured as changes in balloon volume in the proximal colonic barostat balloon. After a basal recording period of 30 min, duodenal perfusion (1.5 ml/min) of lipid (Microlipid; Mead Johnson, Evansville, IN) was performed at 3 kcal/min for 60 min. Recording of colonic tone continued for 1 h after completion of duodenal perfusion. This protocol has been previously validated in our laboratory (5). The amplitude of the lipid-induced colonic response was calculated as the maximal volume decrease for a given 30-min recording segment compared with the basal recording period. Latency of the response was defined as the time in minutes from when the lipid perfusion was started to the time at which a decrease in colonic balloon volume representing 10% of the maximal volume decrease persisted for at least 15 consecutive minutes.

Peristaltic reflex assessment. The orad component of the peristaltic reflex was assessed by the proximal balloon, whereas the distal balloon assessed the caudad response, in both cases after inflation of the middle stimulus balloon using methods previously validated in our laboratory (5, 24). Each recording balloon was inflated to an operating pressure 2 mmHg more than the minimal distending pressure. The peristaltic reflex was evoked by inflation of the middle stimulus balloon with air volumes of 30, 60, and 90 ml at a rate of 30 ml/s. Stimulus inflations were maintained for 30 s and were followed by 5-min intervening periods of deflation to allow colonic tone to return to baseline. The amplitude of the contractile or relaxant response was measured by the difference between the minimal and maximal volume during the inflation period compared with a 30-s preinflation baseline period. A positive ascending or descending contraction was defined as a recording balloon decrease of at least 1 ml occurring during the 30 s of stimulus balloon inflation. Latency of the ascending or descending contraction was defined as the time from the onset of stimulus inflation to the point at which the decrease in proximal or distal balloon volume represented 10% of the maximal response. A positive descending relaxation was defined as a recording balloon volume increase of at least 1 ml in the first 15 s of stimulus balloon inflation. Latency of the descending relaxation was defined as the time from onset of stimulus inflation to the point at which the increase in distal balloon volume represented 10% of the maximal volume increase. Minimal and maximal volume values were obtained with spreadsheet analysis of data acquired in 1-s intervals.

Colonic smooth muscle response to bethanechol. In separate experiments, the effects of the muscarinic receptor agonist bethanechol (Urecholine; Merck, Sharp & Dohme, West Point, PA) were tested in the constipated patients and their response was compared with those of the healthy volunteers. The proximal colonic recording balloon was inflated to a pressure 2 mmHg above the minimal distending pressure. After obtaining a 30-min baseline recording of colonic tone, 5 mg bethanechol was administered subcutaneously. Changes in colonic barostat balloon volume were then recorded for 1 h using methods previously validated (24). The amplitude of the contractile response to bethanechol was determined by subtracting the mean colonic balloon volume in the hour after injection from the mean volume in the 30 min before injection.

Statistical Analysis

Results were expressed as means ± SE. Basal colonic tone, gastrocolonic response latencies, the amplitudes of the duodenal lipid-evoked colonic response, peristaltic reflex latencies, and the amplitudes of the responses to bethanechol were compared using the paired two-tailed Student’s t-test. Repeated-measures ANOVA was performed on the amplitudes of the antral distension-induced gastrocolonic response and the peristaltic reflex to compare responses in each subject group and between granisetron and placebo. Statistical significance was accepted at P < 0.05.

RESULTS

Basal Colonic Tone

All healthy volunteers and patients with slow-transit constipation well tolerated placement of the barostat catheter and did not perceive inflation of the recording balloons in the colon. Mean operating pressures were 11.7 ± 0.9 and 11.5 ± 0.6 mmHg in healthy volunteers and patients, respectively, with minimal interindividual differences. After placebo, mean basal colonic recording balloon volumes were 139 ± 11 ml in healthy volunteers and 182 ± 29 ml in patients (P = not significant; NS). Mean basal colonic recording balloon volumes were unaffected by granisetron (138 ± 16 ml in healthy volunteers, 172 ± 30 ml in patients with constipation; P = NS).

Gastrocolonic Response Assessment

Antral distension. Antral balloon inflation produced decreases in colonic recording balloon volumes, with latencies of onset of the contractile response of 60–90 s (Fig. 1). After placebo infusion, antral distension evoked volume-dependent increases in colonic tone in healthy volunteers with maximal decreases in recording balloon volumes of 35 ± 13 ml with an antral inflation volume of 300 ml (Fig. 2). There were no differences in responses in male versus female healthy volunteers (data not shown). The colonic response to antral distension after placebo was markedly reduced in patients with slow-transit constipation with a maximal decrease in colonic recording balloon volume of 6 ± 6 ml with an antral inflation volume of 300 ml (P < 0.05). Granisetron significantly blunted the increases in colonic tone evoked by antral distension in healthy volunteers (Fig. 2) (P < 0.05). No differences were detectable in the residual antral distension-evoked gastrocolonic response after granisetron administration in healthy volunteers versus patients with slow-transit constipation (P = NS). However, because of the small magnitude of the response in the constipated patients, the effects of granisetron could not be assessed in this subject group.

Duodenal lipid perfusion. Intraduodenal perfusion of lipids (3 kcal/min) evoked reproducible decreases in colonic recording balloon volumes (Fig. 3). These volume changes were significantly decreased in slow-
transit constipated patients compared with the healthy volunteers (Fig. 4). There were no differences in colonic responses in male versus female healthy volunteers (data not shown). As with the antral distension-evoked responses, patients with slow-transit constipation exhibited significantly smaller reductions in colon balloon volume with lipid perfusion than the healthy volunteers after placebo administration (29 ± 15 vs. 64 ± 10 ml, \( P < 0.05 \)) (Fig. 4). Latencies to the onset of the lipid-induced response were similar in both groups (48 ± 15 vs. 49 ± 21 min in healthy volunteers and patients, respectively). Granisetron administration significantly reduced the increase in colonic tone evoked by intraduodenal lipid perfusion in both healthy volunteers and patients with slow-transit constipation (\( P < 0.05 \)) (Fig. 4). Furthermore, the residual duodenal lipid-activated colonic response after granisetron was reduced in the patients with slow-transit constipation compared with the healthy volunteers (\( P < 0.05 \)). Both the 5-HT\(_3\)-dependent component and the residual response after granisetron were reduced in magnitude in slow transit constipated patients compared with the healthy volunteers (\( P < 0.05 \)).

**Peristaltic Reflex Assessment**

In healthy volunteers, inflation of the stimulus balloon in the descending colon evoked reproducible increases in colonic tone proximal to the stimulus (ascending contraction) and a biphasic response distal to the stimulus (descending response) consisting of an initial decrease in tone (relaxation) followed by an increase in tone (contraction) (Fig. 5).

**Ascending responses.** Inflation of the colonic stimulus balloon produced increases in tone orad to the stimulus with latencies of 8 ± 2 s in healthy volunteers. In the...
healthy volunteers, inflation of the stimulus balloon produced volume-dependent decreases in the volume of the proximal colon recording balloon after placebo administration (Fig. 6). There were no differences in the ascending contractile responses in male versus female healthy volunteers (data not shown). Ascending contractile responses to stimulus balloon inflation after placebo were considerably smaller in the patients with slow-transit constipation ($P < 0.05$). Furthermore, three of the patients showed a paradoxical reaction to stimulus balloon inflation exhibiting decreases in colonic tone proximal to the stimulus (Fig. 5). This phenomenon was not observed in any of the healthy volunteers. Granisetron did not affect the ascending contraction response to stimulus balloon inflation in the healthy volunteers ($P = NS$). Given the small magnitude of the ascending contractions in the constipated patients, the effects of granisetron could not be assessed in this subject group.

**Descending responses.** Stimulus balloon inflation produced biphasic responses in the distal colon recording balloon in both the healthy volunteers and the patients with slow-transit constipation with initial relaxations (latency $5 \pm 2$ s) followed by contractions (latency $17 \pm 3$ s) (Fig. 5). After placebo administration, the maximal distal colon volume increase after stimulus balloon inflation to 30 ml was $7 \pm 2$ ml in the
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healthy volunteers (Fig. 7). The maximal distal colon volume decrease after stimulus balloon inflation to 90 ml was 112 ± 17 ml in the healthy volunteers (Fig. 8). There were no significant differences in either response in male versus female healthy volunteers (data not shown). The amplitude of these descending relaxation and contraction responses were similar in healthy volunteers and in patients with slow-transit constipation ($P = $ NS). Granisetron did not affect the descending relaxation or contraction responses to stimulus balloon inflation ($P = $ NS).

Colonic Smooth Muscle Responses to Bethanechol

To test whether the reduced reflex colonic motor activity in patients with slow-transit constipation is caused by defects at the level of the colonic smooth muscle, descending colon tone was measured after subcutaneous administration of bethanechol, an agent that acts directly on smooth muscle muscarinic receptors. Bethanechol injection reduced proximal colon recording balloon volumes by 28 ± 15 ml in the healthy volunteers versus 39 ± 18 ml in patients with slow-transit constipation ($P = $ NS).

Findings of the current investigation significantly enhance our understanding of the abnormalities in reflex colonic motor responses present in patients with slow-transit constipation. We have confirmed previous reports describing impairment of the gastrocolonic response to meal ingestion with constipation (3, 4, 18, 21). Specifically, one investigation demonstrated reduced colonic contractile responses to meal ingestion in patients with slow-transit constipation, whereas individuals with reports of constipation but normal rates of colonic transit exhibited normal gastrocolonic responses (18). However, the gastrocolonic response in healthy humans has been characterized to include two components, a mechanoreceptor-activated component

stimulated by distension of the distal stomach and a chemoreceptor-activated component evoked by exposure of the small intestinal mucosa to nutrient perfusion, especially lipids (5, 30). Our studies expand on prior observations demonstrating that colonic responses to both antral distension and duodenal lipid perfusion are blunted in patients with slow-transit constipation.

Serotonin receptors of the 5-HT$_3$ subtype play a prominent role in both physiological and pathophysiological regulation of colonic motility. Previous investigations have shown that the 5-HT$_3$ receptor antagonist ondansetron blunts the colonic contractile response to eating, confirming mediation of the gastrocolonic response by 5-HT$_3$ receptor pathways (29). We subsequently reported that colonic motor responses to both antral distension and duodenal lipid perfusion are mediated by 5-HT$_3$ receptors despite the differences in the nature of the stimuli and the temporal profiles of the contractile responses (5). The importance of 5-HT$_3$ receptor pathways in the physiological modulation of colonic transit is evidenced by the clinical observations that 5-HT$_3$ receptor antagonists such as ondansetron, granisetron, and alosetron induce pronounced colonic retention in some individuals (1, 2, 6, 9, 27).

In the present investigation, we aimed to test whether defects in the gastrocolonic response associated with slow-transit constipation could be determined to result from selective defects in 5-HT$_3$ receptor-dependent or -independent function or whether the reduced responses stem from more generalized neural dysfunction. In our study, the 5-HT$_3$ receptor antagonist nearly abolished contractile responses to distal gastric distension in healthy volunteers. In contrast, granisetron had no significant effect on the colonic response to antral distension in the constipated pa-

Fig. 7. Cumulative descending relaxation responses to colonic stimulus balloon inflation are shown. Healthy volunteers and patients with slow-transit constipation exhibited increases in caudal recording balloon volumes of similar magnitude unaffected by granisetron administration ($P = $ not significant). Values are means ± SE.

Fig. 8. Cumulative descending contraction responses to colonic stimulus balloon inflation are shown. Healthy volunteers and patients with slow-transit constipation exhibited decreases in caudal recording balloon volumes of similar magnitude that were unaffected by granisetron administration ($P = $ not significant). Values are means ± SE.
tients. However, because the magnitude of the response to antral distension in these individuals is so small, it is impossible with the methodologies employed in the current study to determine whether this defect stems from selective loss of 5-HT3-dependent pathways or generalized loss of neuronal function. As we previously reported, granisetron also blunted the colonic tonic contractile response to duodenal lipid perfusion in the present investigation; however, this inhibition was less complete (5). Patients with slow-transit constipation exhibited significant reductions in the total, granisetron-sensitive, and granisetron-insensitive colonic responses to lipid perfusion. These results suggest that, with respect to the lipid-activated colonic response, there is a generalized defect in reflex neural activity to the colon involving 5-HT3 receptor-dependent and -independent pathways.

In addition to external influences, colon motor function is modified by stimuli within the colonic lumen. The best characterized local motor response, the peristaltic reflex, consists of an orad ascending contraction and a caudad descending relaxation as measured in ex vivo models (8, 10, 12–14, 26). In our previous investigations, we demonstrated an additional descending contractile response that follows descending relaxation (5, 24). In isolated human small intestine, serotonin released by mechanical stimulation is proposed to act on 5-HT3/5-HT1P receptors to initiate the peristaltic reflex (8, 11, 19). 5-HT3 receptors appear to participate prominently in the peristaltic reflex only in nonhuman species such as the guinea pig (8). As characterized in our previous investigation, granisetron did not affect the amplitudes or latencies of the ascending contraction or the descending relaxation or contraction in the current study, indicating that 5-HT3 receptors are not the major mediators of the colonic peristaltic reflex in the intact human (5). In the present investigation, patients with slow-transit constipation exhibited marked reductions in the amplitude of the ascending contraction. This component of the peristaltic reflex has been proposed to provide an aborally propulsive force to move intraluminal contents in a caudal direction. Thus impairment of this arm of the reflex would have pathophysiological importance in idiopathic constipation. In contrast, patients with slow-transit constipation exhibited no abnormalities of either the descending relaxation or contraction. The descending relaxation has been proposed as an accommodative phenomenon that facilitates aboral migration of the fecal bolus. Based on the findings of the present study, it appears that this physiological response remains intact in patients with slow-transit constipation.

An additional abnormality of the ascending component of the peristaltic reflex was observed in a minority of our patients with slow-transit constipation. Three patients exhibited an initial orad relaxation in response to inflation of the colonic stimulus balloon. Colonic transit times in these three individuals were not obviously different from the other patients who did not exhibit ascending relaxation responses. However, given the small number of patients studied, a statistical comparison between patients with oral relaxation versus those with oral contraction was not possible. These observations suggest that the pathophysiological abnormalities that produce slow-transit constipation may be heterogeneous. Furthermore, this may indicate that the therapy of severe slow-transit constipation may need to be tailored to the motor defect that is characterized by careful physiological testing.

Findings of the present investigation indicate that the impairment of colonic motor function in patients with slow-transit constipation is secondary to neural dysfunction and that it does not stem from a reduction of contractile efficacy at the smooth muscle level. Descending contractile response in the constipated patients was similar to that of the healthy volunteers. Furthermore, increases in colonic tone in response to the smooth muscle muscarinic agonist bethanecol were not reduced in the patients with slow-transit constipation.

Although we have demonstrated that the 5-HT3-dependent gastrocolonic response to antral distension is impaired in slow-transit constipation, it is conceivable that neural responses mediated by other receptor populations also may be impaired in these patients. 5-HT4 receptors, α2-adrenoceptors, and others may play important roles in local peristaltic (or retroperistaltic) activity. These are worthy of future investigation. It is also important to point out that this investigation was performed only in women with slow-transit constipation. There was no difference in either gastrocolonic responses or peristaltic reflex activities in healthy men or women, thus the responses observed in the women with slow-transit constipation did not stem from a gender effect. However, a minority of patients with slow-transit constipation are men. It would be interesting to determine whether similar physiological abnormalities are present in constipated men.

In conclusion, patients with idiopathic slow-transit constipation exhibited impairment of the colonic responses to antral distension and duodenal lipid perfusion. Reductions in the response to lipids involve nonselective deficits in both 5-HT3 receptor-dependent and -independent pathways. These patients also showed blunting of the ascending contractile component of the colonic peristaltic reflex, whereas the descending components of the peristaltic reflex were unaffected. Some patients demonstrated an additional defect, an orad relaxation response to colonic distension. Colonic tonic responses to smooth muscle muscarinic receptor activation were not reduced in constipated patients, indicating that impaired contractile activity results from neuronal dysfunction rather than a smooth muscle defect. We believe that these abnormalities of neural reflex modulation of colonic motor function may play pathophysiological roles in development of slow-transit constipation.

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